REMARKS

Amendments to the specification represent the addition of information designating the depository, accession number, and deposit date of the deposited BHK-RR-B51E and HeLa-RR-B51S cell line in ATCC as per the requirements of 37 CFR 1.809(d). The insertion of such information in the specification after the filing date does not violate the prohibition against new matter in 35 U.S.C. §132 (see MPEP §2406.01, citing *In re Lundak,* 773 F.2d 1216, 227 USPQ 90 (Fed. Cir. 1985)).

Claims 1-32 were presented in the original application. Claims 20-32 were cancelled by Applicants in their Election and Reply to Restriction of December 4, 2007. Claims 1, 8, and 16 are currently amended. Support for the amendments to Claims 1 and 16 can at least be found on Page 6, lines 26-29 (for "sequences encoding the F, G and SH glycoproteins") and on Page 12, line 32 to Page 13, line 7 (for "and wherein said replicon is non-cytotoxic to said cells when said cells do not express F, G, and SH viral glycoproteins").

INTERVIEW SUMMARY

On July 15, 2008, the Applicants' representatives Charles Romano and William Holtz conducted a telephonic interview with Examiner Stuart Snyder. Applicants explained that the proposed amendment of claims 1 and 16 to recite "non-cytotoxic replicons when said cells do not express F, G, and SH viral glycoproteins" renders the claims definite under 35 USC § 112 as the cytotoxicity reported in the cited art occurred in cells that express one or more of these glycoproteins. Proposed amendments to independent Claim 1 and 16 directing these to a respiratory syncytial virus (RSV) replicons were also discussed in light of the 35 USC § 102

rejections over references that disclose Sendai virus replicons. Applicants also indicated that the outstanding 35 USC § 103 obviousness rejections would be addressed by pointing out teaching away by certain cited references and evidence of unexpected results as indicia of non-obviousness. Examiner indicated that Applicants should stress evidence of unexpected results in their response.

In a subsequent telephonic conversation on July 15, 2008, Examiner Snyder communicated to Charles Romano the comments of Supervisory Patent Examiner Mosher, indicating that recitation of cell line deposit numbers in claim 14 would necessitate amendments that would render the Specification compliant with 37 CFR § 1.809 and would require availability statements compliant with 37 CFR § 1.808.

NOVELTY REJECTIONS UNDER 35 USC §102

The Examiner has rejected previously pending claims 1-2, 4-6, and 16-19 under 35 USC §102(b) as anticipated by DNAVEC Research, Inc (WO 00/70070), which was alleged to disclose Sendai virus replicons deficient in both F and HN (the sole glycoproteins of the virus). The claims as currently amended are directed to respiratory syncytial virus (RSV) replicons and are thus not anticipated by DNAVEC Research, Inc. Examiner also rejected previously pending claims 1-2 and 4-6 under 35 USC §102(e) as anticipated by Kitazato et al., (U.S. Patent 7,226,786), which was alleged to disclose Sendai virus replicons deficient in both F and HN (sole glycoproteins of the virus). As stated above, the claims as currently amended are directed to respiratory syncytial virus (RSV) replicons and are thus not anticipated by Kitazato et al. Applicants thus respectfully request that the rejections of the currently pending claims under 35

USC §102 as anticipated by DNAVEC Research, Inc and as anticipated by Kitazato et al., be withdrawn.

OBVIOUSNESS REJECTIONS UNDER 35 USC §103

The claims are not obvious because prior art does not teach or suggest all of the claim limitations.

The Examiner has rejected previously pending claim 3 under 35 USC §103 as obvious over DNAVEC Research, Inc (WO 00/70070), which was alleged to disclose Sendai virus replicons, in view of Kimura, et al., (Mol. Gen. Genet. 242: 121-1 29, 1994), which was alleged to disclose *bsd* genes. Claim 3 as currently amended is directed to respiratory syncytial virus (RSV) replicons that comprise a *bsd* gene. To establish a prima facie case of obviousness, cited references must teach or suggest all of the claim limitations (see MPEP §2143.03 and citations of *In re Wilson*, (424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970) and *In re Royka*, (490 F.2d 981, 180 USPQ 580 (CCPA 1974) therein). Neither DNAVEC Research, Inc. or Kimura et al., teach RSV replicons as specified by the currently amended claim 1 and dependent claim 3. Since all limitations of the currently amended claims are not taught or suggested by either DNAVEC Research, Inc., Kimura et al., or their combination, the Examiner is respectfully requested to withdraw this obviousness rejection.

The prior art considered as a whole fails to establish a prima facia case of obviousness.

The Examiner has rejected previously pending claims 7-13 and 15 under 35 USC §103 as obvious over DNAVEC Research, Inc (WO 00/70070), which was alleged to disclose Sendai virus replicons, in view of Kimura, et al., (Mol. Gen. Genet. 242: 121-1 29, 1994), which was alleged to disclose *bsd* genes, and further in view of Nagai and Kato (Microbiol. Immunol. 42(7):

613-624, 1999). Nagai and Kato is alleged to teach that "genes of related negative strand RNA viruses can substitute for one another, especially in the case of related paramyxovirus surface proteins " and that such exchange leads to different host susceptibility as well as deletion or mutations of analogous genes leads to attenuation of virus virulence in the intended host species". The examiner further alleges that:

> Given the success of such approached in the related Sendai viruses, a skilled artisan would have a reasonable expectation of success transferring such methods to RSV with the exception that the additional protein SH of RSV would necessarily be deleted in the attenuated RSV replicon because it is also involved in cell entry and fusion events of RSV, as taught by Nagai and Kato.

In considering the Examiner's rejection under 35 USC §103 as obvious over DNAVEC Research, Inc., Kimura, et al., (Mol. Gen. Genet. 242: 121-1 29, 1994), and Nagai and Kato (Microbiol. Immunol. 42(7):613-624, 1999), Applicants first note the Examiner's obligation to consider the prior art as a whole, including portions that would lead away from the claimed invention (See MPEP §2141.02, section IV, citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). More specifically, Nagai and Kato, in the section entitled "Live Vaccines"(p. 619 to 620) teach "The V and C knockout SeVs conferred protective immunity in mice, suggesting their potential use as live vaccines (Kiyotani et al., unpublished). The same has been suggested for several knockout RSVs, in which *each* of the SH, NS1, NS2, and G genes was *deleted individually* (reviewed in 12)" (*emphasis added).* Thus, Kato and Nagai teach vaccines that delete only a *single gene*, whereas the currently claimed RSV replicons comprise RSV viruses where *three genes* (F, SH,

and G) are inactivated or deleted. Although the Examiner may maintain that this teaching of Kato and Nagai is somehow negated by the teachings of DNAVEC Research, Inc., these cited references contain inconsistent and conflicting teachings. The prior art thus fails to support a *prima facie* case of obviousness as it includes portions that would lead away from the claimed invention when considered as a whole.

One skilled in the art would not have had a reasonable expectation of success.

Applicants further note that the Examiner has an obligation to establish a reasonable expectation of success in rejecting the claims as obvious over DNAVEC Research, Inc., Kimura, et al., (Mol. Gen. Genet. 242: 121-1 29, 1994), and Nagai and Kato et al., (see MPEP § 2143.02, citing *KSR International Co. v. Teleflex Inc.,* 550 U.S. ___, ___, 82 USPQ2d 1385, 1395 (2007); and *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). While DNAVEC Research, Inc., allegedly discloses Sendai virus replicons deficient in the sole glycoproteins of the virus (i.e. both F and HN), as noted above, Kato and Nagai describe deletion of only a single gene. The conflict of these teachings is evidence of uncertainty in the art that rebuts the Examiner's allegation that one skilled in the art would have a reasonable expectation of success. To the contrary, one of skill in the art would be unsure whether deletion of all or only one of the viral glycoproteins would be successful. The field of molecular biology is unpredictable, and it is understood by those skilled in the art—and demonstrated by the Applicants as described below—that those modifications that may work for one viral genome don't necessarily transfer to other even closely related viruses. Because Applicants believe that they have cited evidence that properly rebuts the Examiner's obligation to establish a reasonable expectation of success, the Examiner is respectfully requested to withdraw this obviousness rejection.

Applicants' evidence of unexpected results rebuts Examiner's rejection of the claims as obvious.

According to the Examiner, all that would be required by a highly motivated skilled artisan to produce a reduced virulence RSV replicon would be to transfer the approach as taught by Nagai and Kato to RSV, with the exception that SH of RSV would also be deleted. However, in Example 1 of the Specification as filed, Applicants disclose experiments testing replication of F, G, and SH glycoprotein-deleted RSV in cultured cells. According to the Examiner, one skilled in the art would expect such an experiment to be successful. Applicants however were unable to obtain isolated cells that contained F, G, and SH glycoprotein-deleted RSV replicons and suggested that "in the absence of the glycoprotein genes, RSV is cytotoxic, though relatively slowly" (Final paragraph of Example 1). Given the result that the F, G, and SH glycoprotein-deleted RSV replicons were cytotoxic, Applicants subsequent recovery of F, G, and SH glycoprotein-deleted RSV replicons that further comprised a selectable marker and that were non-cytotoxic in Examples 2 and 3 is evidence of an "unexpected result." (*see* MPEP § 2141 section V: Rebuttal evidence may include evidence of "secondary considerations," such as "commercial success, long felt but unsolved needs, [and] failure of others" (*Graham v. John Deere Co.*, 383 U.S. at 17, 148 U.S.P.Q. at 467) and may also include *evidence of unexpected results*.) (emphasis added).

In light of Applicants' evidence of unexpected results, Applicants believe that any rationale for obviousness has been negated and therefore the Examiner is respectfully requested to withdraw this obviousness rejection.

DOUBLE PATENTING

The Examiner has rejected claims 1, 4-9, 13, and 16-19 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,270,958 issued August 7, 2001 ('958 Patent). Applicants have obviated the nonstatutory double patenting rejection by filing a Terminal Disclaimer for the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior U.S. Patent No. 6,270,958 under the provisions of 37 C.F.R. § 1.321.

REJECTIONS UNDER 35 USC §112, FIRST AND SECOND PARAGRAPHS

The Examiner has rejected currently pending claims 1-19 under 35 USC § 112, first paragraph, as failing to comply with the enablement requirement and similarly rejected claims 1-19 under 35 USC § 112, second paragraph, as being indefinite. In either case, the Examiner states:

> Independent claim 1 and 16 each recite "non-cytotoxic" replicons; the specification does not define "non-cytotoxic" nor does it limit the requirement to a specific cell type. Previous work by some of the Applicants as well as others (see, for example, Applicant cited art, Oomens, et al., Tchaarpornkul, et al., and non-patent literature cited by Whelan) wherein SH, F and G deleted replicons were "rescued" in cell-lines expressing some or all of the deleted RSV proteins resulting in expression of lytic RSV.

The Examiner alleges, "Applicant's replicons produced in the examples are indeed cytotoxic, although only in a limited number of cell-lines," (Office Action page 7) and "[t]hus, the limitation of "non-cytotoxic" does not clearly define Applicant's claimed invention" (Office Action page 8). Applicants have currently amended claims 1 and 16 to read "wherein the replicon can be used to biologically select cells containing stable, replicating, non-cytotoxic replicons when said cells do not express F, G, and SH viral glycoproteins". As noted by the Examiner, the replicons produced were cytotoxic, "although in a limited number of cells lines." These cells lines wherein the replicons were cytotoxic were cell lines expressing viral glycoproteins. Thus, the current modifications to the claims make clear that the replicons are non-cytotoxic in cells that "do not express F, G, and SH viral glycoproteins." Therefore the meaning of "non-cytotoxic" would be clear to one of skill in the art as pertaining to cells type not expressing F, G, and SH viral glycoproteins. One of skill in the art would consider such a meaning entirely consistent with the possibility that cytotoxicity could be observed in other cell types expressing the specified viral glycoproteins.

In light of the clarifying modifications made and the reasoning set forth above, Applicants respectfully request that the rejections of the currently pending claims under 35 USC §112, paragraphs 1 and 2, as either non-enabled or indefinite respectively be withdrawn.

COMPLIANCE WITH DEPOSIT RULES OF 37 CFR § 1.808 AND 37 CFR § 1.809

In the telephonic interviews of July 15, 2008, the Examiners indicated that claim 14, which recites specific cell line deposits, requires a promise for availability. As the Applicant's agent, and having received signed assurances from the Applicants, the undersigned represents

that both the deposit with the ATCC of the cell line BHK-RR-B51E accorded the accession number number PTA-5257 and the deposit of the cell line HeLa-RR-B51S accorded the deposit number PTA-5258 were made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent. Applicant's believe that the above statement by an agent of record over the agent's signature satisfies in part the deposit requirements of 37 C.F.R. § 1.808.

Applicants have also currently amended the specification in compliance with 37 C.F.R. §1.809(d) so as to identify the accession numbers of the deposits, the date of deposit, a description of the deposited materials, and the complete name and address of the depository. Applicants thus believe that this amendment to the specification clearly indicates the public availability of the deposited cell lines that harbor the replicons of claim 14 and places the application in compliance with 37 C.F.R. §1.809(d).

CONCLUSION

It is not believed that extensions of time are required beyond those, which may otherwise be provided for in the filing of this Amendment. However, in the event that additional extensions of time or other fees are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned for under 37 C.F.R. §1.136(a), and any fees required are hereby authorized to be charged to our Deposit Account No. 20-0823.

The Examiner is encouraged to contact the undersigned via telephone at the number provided, if it is determined that personal communication will expedite prosecution of this application.

Respectfully submitted,

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